

MS APPEAL BRIEF
PATENT
2503-1225

**IN THE U.S. PATENT AND TRADEMARK OFFICE BEFORE
THE BOARD OF PATENT APPEALS AND INTERFERENCES**

In re application of	Appeal No.
Paolo MORAZZONI et al.	Conf. 5191
Application No. 10/587,468	Group 1655
Filed November 27, 2006	Examiner Qiuwen Mi

USE OF A GINKGO COMPLEXES FOR THE ENHANCEMENT OF COGNITIVE
FUNCTIONS AND THE ALLEVIATION OF MENTAL FATIGUE

APPEAL BRIEF

MAY IT PLEASE YOUR HONORS:

Applicants respectfully appeal the Final Rejection of
claims 23, 26-42 and 46 as unpatentable under 35 U.S.C. 103(a) as
set forth in the Official Action mailed December 30, 2010.

(1) Real Party in Interest

The real parties in interest in this appeal is the assignee INDENA S.P.A., Milano, Italy.

(2) Related Appeals and Interferences

None.

(3) Status of Claims

Claims 23 and 26-46 are pending in this application. Claims 1-22, 24-25 and 43-45 have been canceled. Claims 43-45 are withdrawn.

Claims 23, 26-42 and 46 are rejected, from whose final rejection this appeal is taken.

(4) Status of Amendments

A Final Office Action was mailed on December 30, 2010. An Amendment After Final Rejection was filed on March 30, 2011, and the amendments were entered for purposes of appeal as evidenced by the Advisory Action of April 7, 2011. No Amendments have been filed subsequent to the March 30, 2011 Amendment.

(5) Summary of Claimed Subject Matter

The claims are directed to methods for enhancing cognitive function and alleviating mental fatigue in a subject by administering a complex of ginkgo and phospholipid, the phospholipid having 20% phosphatidylserine. The claims are also directed to methods for improving memory speed and memory quality in normal healthy humans, reducing deterioration of memory speed and memory quality in people with decreased cognitive functions, and treating diseases related to reduced cognitive function and mental fatigue such as dementia and Alzheimer's disease, by administering ginkgo complexed with phosphatidylserine.

Present claim 23 is directed to a method for enhancing cognitive function and alleviating mental fatigue comprising administering ginkgo complexed with phospholipid containing 20% phosphatidylserine. Support for each feature of claim 23 can be found in the specification in the Abstract; at page 3, lines 16-23; and at page 8, lines 7-9. Claims 26-34 and 46 depend from claim 23 and stand together with claim 23.

Present claim 35 is directed to a method for improving memory speed and memory quality in a healthy human, or reducing memory speed and memory quality in a human with decreased cognitive functions, comprising administering ginkgo complexed with phosphatidylserine. Support for each feature of claim 35 can be found in the specification in the Abstract; at page 3, lines

24-26; at page 4, lines 6-13; and at page 8, lines 7-9. Claim 35 stands alone.

Present claim 36 is directed to a method for treating a disease related to reduced cognitive function and increased mental fatigue, comprising administering ginkgo complexed with phosphatidylserine. Support for each feature of claim 36 can be found in the specification in the Abstract; at page 3, lines 16-23; and at page 8, lines 7-9. Claims 37-42 depend from claim 36 and stand together with claim 36.

(6) Grounds of Rejection to be Reviewed on Appeal

A first issue for review is whether claims 23, 26, 29-40 and 46 were properly rejected under 35 U.S.C. § 103(a) as being unpatentable over PHYSIOLOGICS (Phosphatidylserine complex with Ginkgo, "PHYSIOLOGICS") in view of BOMBARDELLI (EPA 0275005, "BOMBARDELLI").

A second issue for review is whether claims 23, 26-41 and 46 were properly rejected under 35 U.S.C. § 103(a) as being unpatentable over PHYSIOLOGICS and BOMBARDELLI and further in view of LOEW (Wiener medizinische Wochenschrift (1946), "LOEW").

A third issue for review is whether claims 23, 26, 29-40, 42 and 46 were properly rejected under 35 U.S.C. § 103(a) as being unpatentable over PHYSIOLOGICS and BOMBARDELLI and further in view of KIM et al. (FASEB Journal, March 2003, Vol. 17, No. 4-5, "KIM").

(7) Arguments

Ginkgo is believed to have nootropic properties and has been used as a memory and cognitive enhancer. The active ingredients of ginkgo extracts include flavonoid glycosides, terpenoids, alkylated phenols such as ginkgol and 3-(8-pentadecenyl) phenol, and phenolic carboxylic acids such as 2-hydroxy-6-(8-pentadecenyl) benzoic acid, ginkgolide and bilobalide (see, page 1, lines 12-18). There have been a variety of studies on the influence of *Ginkgo biloba* extract on cognitive performance (see, page 2, lines 15-24). The effects according to the presently claimed methods, however, are superior to anything previously described in the art.

The present invention refers to the use of ginkgo formed in a complex with phosphatidylserine. The complex of ginkgo and phosphatidylserine is obtained by reacting an extract of ginkgo with a phospholipid containing phosphatidylserine (see, page 6, lines 14-21; page 9, lines 10-13). The resulting complex exhibits a greater activity as compared to ginkgo in free form and is suitable for incorporation in common pharmaceutical formulations (see, page 9, lines 2-4). More specifically, a complex of ginkgo and phospholipid significantly enhances cognitive function and reduces mental fatigue to a much greater extent than that provided by the mere combination mixture of ginkgo and phospholipid.

Forming complexes of ginkgo and phospholipid provides new biologically active compositions having physico-chemical and spectroscopic characteristics that are markedly different from those of the original components. Additional details provided by U.S. Patent No. 5,043,323 (fully incorporated by reference in the present application, at page 6, lines 11-13) indicate that in the formation of the complexes, the polar head of the phospholipid is directly involved in the complex while the fatty acid moieties retain a high degree of mobility, conferring marked lipophilia to the new molecule.



ginkgo-phospholipid

7.1 PHYSIOLOGICS & BOMBARDELLI

The Office takes the position that PHYSIOLOGICS teaches a composition comprising a phospholipid complex containing 20% phosphatidylserine and *Ginkgo biloba* extract that is advertised to treat mild memory problems associated with aging. The PhysioLogics product, however, is not a complex of ginkgo with phosphatidylserine that is the subject matter of the present claims.

As clearly specified on the product label, the PhysioLogics product, "Phosphatidylserine Complex with Ginkgo," is merely a mixture of *Ginkgo biloba* and phospholipids, i.e., it is not a complex of ginkgo with phosphatidylserine. This is an

important distinction between the compositions of the present

claims and that of PhysioLogics. The PhysioLogics product is not a complex of ginkgo-phosphatidylserine as defined in the specification.

Supplement Facts		
Serving Size 1 softgel		
Amount Per Serving	%Daily Value	
Vitamin C (as Ascorbic Acid)	5 mg	8%
Neuro-PS™	500 mg	*
(Phospholipid Complex from Soy Lecithin)		
(standardized to contain 20% Phosphatidylserine, 100 mg)		
which typically provides:		
Phosphatidic Acid, Phosphatidylinositol, Soy Phospholipids & Glycerides, Phosphatidylcholine, Phosphatidylethanolamine	300 mg	*
Ginkgo Biloba Extract	30 mg	*
(standardized to contain 24% Ginkgo Flavone Glycosides, 7.2 mg)		
*Daily Value not established.		

Other Ingredients: Gelatin, Glycerin, Lecithin, Yellow

The Office Action recognizes that the PHYSIOLOGICS product is not a complex of ginkgo-phosphatidylserine as defined by the present specification and claims, and acknowledges that PHYSIOLOGICS does not teach or suggest a complex of ginkgo-phosphatidylserine. The Office relies on BOMBARDELLI for teaching this aspect.

BOMBARDELLI broadly describes compositions of various flavonoids complexed with phospholipids. BOMBARDELLI discloses that flavonoids possess a number of recognized pharmacologic properties such as anti-inflammatory, antispasmodic, antihistaminic, vasodilatory, platelet anti-aggregating and antiallergic properties (see, col. 1, lines 25-30). The flavonoids can be applied topically or per os but flavonoids are also known to be very poorly absorbed (see, col. 1, lines 44-53). Thus, BOMBARDELLI addresses this problem by reacting the

flavonoids with phospholipid to form complex compounds having improved lipophilic properties (see, column 1, lines 61-63).

BOMBARDELLI determined that these "complex compounds" possess higher bio-availability for topical formulations. In topical applications, the compounds were 2-4 times as active as the substances administered in free form (see, col. 3, lines 23-27). In particular, BOMBARDELLI discloses that a complex of *Ginkgo biloba* and phosphatidyl choline had improved vasodilatory activity (see, Table 1) and improved antiedematous activity (see, Table 2) when topically applied. BOMBARDELLI then suggests that the compounds could provide increased blood flow at the cutaneous level and may be useful in cosmetic applications. BOMBARDELLI further suggests that the flavonoids may have fibroblast proliferation stimulating activity and therefore may be useful in dermatology for ulcer healing and in cosmetic treatments such as collagen production (see, col. 4, lines 1-7).

BOMBARDELLI fails to teach or suggest, however, that flavonoids would have any effect on enhancing cognitive functions or alleviating mental fatigue, or for improving memory speed and memory quality, or for treating any disease related to reduced cognitive function and increased mental fatigue, which is the featured subject matter of the present claims. More particularly, BOMBARDELLI fails to recognize that a complex of *Ginkgo biloba* extract with phosphatidylserine has any significant effects above a complex of ginkgo-phosphatidylcholine.

One of ordinary skill in the art, in view of the teachings of PHYSIOLOGICS and BOMBARDELLI, would have no reason to select a complex of ginkgo-phosphatidylserine in order to achieve the desired therapeutic purpose - enhancing cognitive function and alleviating mental fatigue, improving memory speed and memory quality, reducing deterioration of memory speed and memory quality, or treating a disease related to reduced cognitive function and increased mental fatigue. Indeed, applicants have demonstrated that a complex of ginkgo-phosphatidylserine provides superior results in cognitive function when compared to the complex of ginkgo-phosphatidylcholine disclosed in BOMBARDELLI.

As detailed in the present specification, in the cognitive assessment tests and results section, a complex of *Ginkgo biloba* extract with phosphatidylserine has outstanding effectiveness compared to both the non-complexed ginkgo as well as to a complex of ginkgo-phosphatidylcholine. (See, Quality of Memory, Picture Recognition Accuracy, Speed of Memory, Timed Memory Tasks, and other tasks concerning attention, page 16, line 16 to page 29, line 5; and Figures 1-6, reproduced below). Crucially, in essentially every aspect tested, the complex of ginkgo-phosphatidylserine performed better than the complex of ginkgo- phosphatidylcholine.

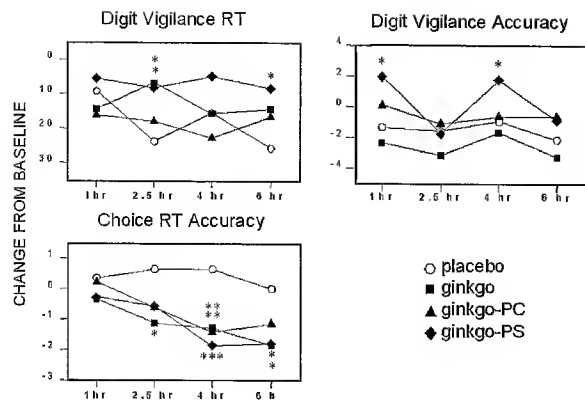


FIG. 1

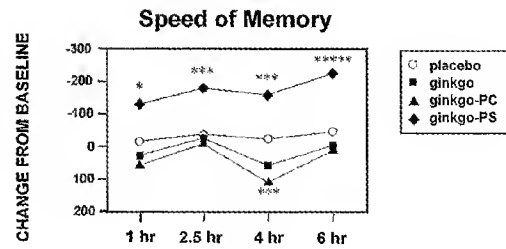


FIG. 2

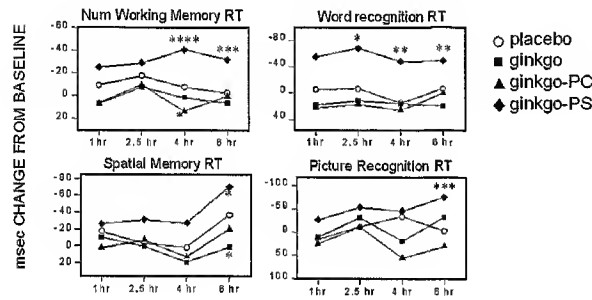


FIG. 3

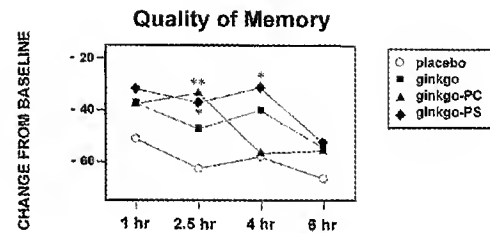


FIG. 4

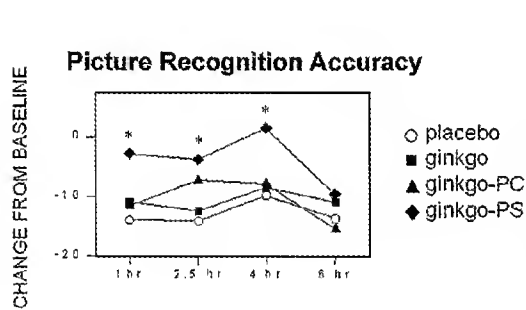


FIG. 5

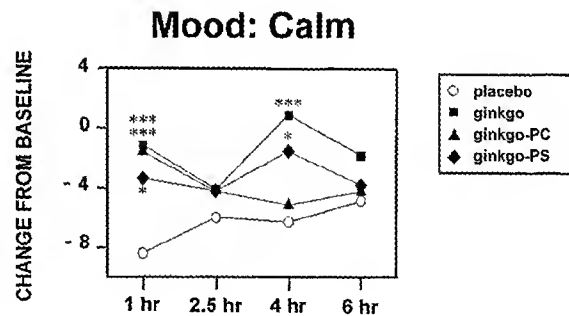


FIG. 6

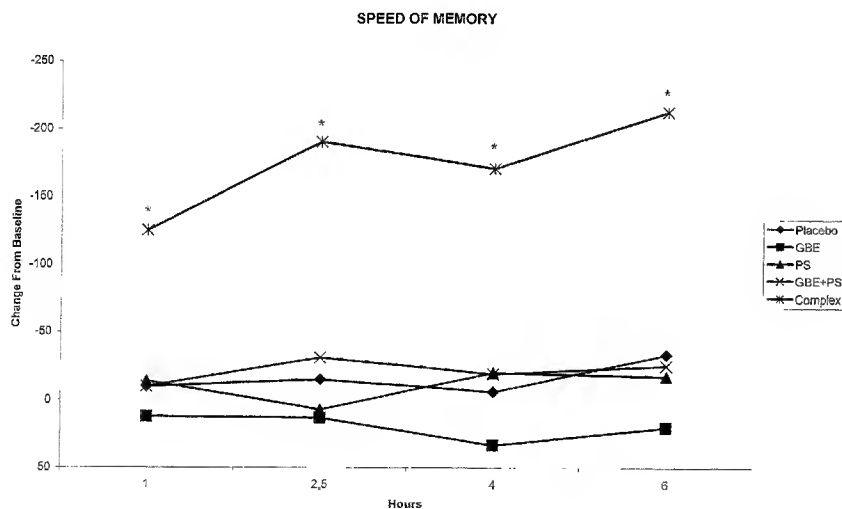
One of ordinary skill in the art, in view of the teachings of PHYSIOLOGICS and BOMBARDELLI, would have no reason to select phosphatidylserine in order to achieve the desired therapeutic purpose - enhancing cognitive function and alleviating mental fatigue, improving memory speed and memory quality, reducing deterioration of memory speed and memory

quality, or treating a disease related to reduced cognitive function and increased mental fatigue. Applicants have demonstrated that a complex of ginkgo-phosphatidylserine provides superior results in cognitive function when compared to the complex of ginkgo-phosphatidylcholine disclosed in BOMBARDELLI.

Indeed, BOMBARDELLI includes only a single specific reference to phosphatidylserine in the entire disclosure, and that is in the claims. In claim 1, BOMBARDELLI lists phosphatidylserine as one of a list of possible phospholipids that includes soy lecithin, egg lecithin, phospholipids from bovine or swine brain or dermis, phosphatidyl choline, and phosphatidyl ethanolamine. Claim 1 also features an extensive list of the various possible flavonoids to use in the complex combination. Then, in the Examples, BOMBARDELLI includes complexes of phosphatidylcholine and phosphatidylethanolamine (see, Examples 1-12) but fails to include any examples of a complex with phosphatidylserine. Thus, BOMBARDELLI fails to teach or suggest anything that would have led one of ordinary skill in the art to expect the superior results obtained specifically from the complex of phosphatidylserine with ginkgo, for the cognitive and mental treatment methods featured in the present claims.

Further support for the unexpectedly superior results of a complex of ginkgo with phosphatidylserine is provided in the Rule 132 Declaration of Ezio Bombardelli, which is of record and was submitted with the May 29, 2009, Amendment. The Declaration

includes the results of experiments carried out on 15 subjects, each subject treated with capsules respectively containing: *Ginkgo biloba* extract (GBE); phospholipids containing 20% phosphatidylserine (PS); mechanical mixtures containing *Ginkgo biloba* extract and phosphatidylserine (GBE + PS); and complexes of *Ginkgo*-phosphatidylserine (Complex). The results show that capsules containing the complex of *Ginkgo* with phosphatidylserine show a remarkably higher and statistically meaningful activity than that of capsules filled with *Ginkgo biloba* extract, phosphatidylserine, or mixtures of *Ginkgo biloba* extract and phosphatidylserine. The results of Speed of Memory tests from the Declaration are reproduced in the following graph.



Thus, the presently claimed methods for enhancing cognitive function, alleviating mental fatigue, improving memory speed and memory quality, reducing deterioration of memory speed and memory quality and treating diseases related to reduced

cognitive function and mental fatigue, by administering a complex of ginkgo with phosphatidylserine would not have been obvious to one of ordinary skill in the art from the teachings of BOMBARDELLI.

7.2 PHYSIOLOGICS, BOMBARDELLI & LOEW

With regard to the secondary references cited in the Office Action, LOEW and KIM each fail to teach or suggest the unexpected results of a complex of ginkgo-phosphatidylserine for the cognitive and mental treatment methods featured in the present claims.

LOEW provides additional details regarding the components of a ginkgo extract but does nothing to remedy the deficient teachings of PHYSIOLOGICS and BOMBARDELLI and fails to teach or suggest the unexpected results of a complex of ginkgo-phosphatidylserine.

7.3 PHYSIOLOGICS, BOMBARDELLI & KIM

KIM describes the health benefits from botanicals such as grape seed extract due to the anti-oxidant activity of polyphenols and proanthocyanidins. KIM also fails to teach or suggest the unexpected results of a complex of ginkgo-phosphatidylserine for the cognitive and mental treatment methods featured in the present claims.

In view of the above remarks, each of the rejections of claims 23, 26-42 and 46 under 35 U.S.C. § 103(a) as being unpatentable over a combination of PHYSIOLOGICS, BOMBARDELLI, LOEW and/or KIM, is improper and should be reversed. Accordingly, Applicants respectfully request reversal of the rejections.

The Appeal Brief fee of \$540.00 is being paid online simultaneously herewith by credit card.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future submissions, to charge any underpayment or credit any overpayment to Deposit Account No. 25-0120 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17.

Respectfully submitted,

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Enclosures: Claims Appendix
Evidence Appendix

(8) Claims Appendix

23. A method for enhancing cognitive function and alleviating mental fatigue in a subject, comprising administering to a subject in need thereof an effective amount of a Ginkgo-phospholipid complex, said complex comprising Ginkgo complexed with a phospholipid, said phospholipid comprising 20% phosphatidylserine.

26. The method according to claim 23, wherein the Ginkgo is derived from the plant *Ginkgo biloba*, extracts thereof and/or one or more principal active substances thereof.

27. The method according to claim 26, wherein one of the principal active substances is bilobalide.

28. The method according to claim 26, wherein the Ginkgo extract comprises at least 20% Ginkgo flavone glycosides and 2-10% terpene lactones.

29. The method according to claim 23, wherein the Ginkgo and the phosphatidylserine in the complex are in a ratio of about 1:3.

30. The method according to claim 23, wherein the Ginkgo-phospholipid complex is in a medicament or a dietary supplement that is administered to the subject in the form of tablets, granules, powders, capsules, syrups, solutions, suspensions, dragees, gels, injections or drops.

31. The method according to claim 23, wherein the Ginkgo-phospholipid complex is in a medicament or a dietary supplement and is formulated for oral administration.

32. The method according to claim 23, wherein the Ginkgo-phospholipid complex is in a medicament or a dietary supplement that is administered in an amount of about 20-240 mg per day.

33. The method according to claim 23, wherein the Ginkgo-phospholipid complex is in a medicament or a dietary supplement, and further comprises a pharmaceutically acceptable amount of at least one additive selected from the group consisting of minerals, vitamins, sweeteners, flavors, pharmaceutically acceptable carriers, auxiliary and binder agents, excipients and mixtures thereof.

34. The method according to claim 33, wherein the additive is selected from the group consisting of calcium,

fluorine, phosphorus, copper, potassium, manganese, magnesium selenium, zinc and iron, Vitamin A, Vitamins B1, B2 and B12, Vitamin C, Vitamin D2, nicotinamide, calcium pantotenate, rutoside and Vitamin E.

35. A method for improving memory speed and memory quality in a normal, healthy human, or reducing deterioration of memory speed and memory quality in a human with decreased cognitive functions, comprising administering to a subject in need thereof an effective amount of Ginkgo complexed with phosphatidylserine.

36. A method for treating a disease related to reduced cognitive function and increased mental fatigue in a subject, comprising administering to a subject in need thereof an effective amount of Ginkgo complexed with phosphatidylserine.

37. The method according to claim 36, wherein the disease is Dementia.

38. The method according to claim 36, wherein the disease is Alzheimer's Disease.

39. The method according to claim 36, wherein the Ginkgo-phosphatidylserine complex is in a medicament or a dietary

supplement, and further comprises a pharmaceutically acceptable amount of at least one additive selected from the group consisting of vitamins, minerals, sweeteners, flavors, pharmaceutically acceptable carriers, auxiliary and binder agents, excipients and mixtures thereof.

40. The method according to claim 36, further comprising administering an additional pharmaceutical compound used for treating the disease related to reduced cognitive function and increased mental fatigue.

41. The method according to claim 40, wherein the additional pharmaceutical compound is an acetylcholinesterase inhibitor.

42. The method according to claim 36, further comprising administering complexed grape seed extract, as an additionally active compound, to the subject.

46. The method according to claim 23, wherein the Ginkgo and phosphatidylserine in the complex are in a ratio of 0.5-1 : 2-5.

(9) Evidence Appendix

Declaration under 37 CFR 1.132 of Ezio Bombardelli

(10) Related Proceedings Appendix

None.